REMARKS

The claims are rejected under 35 U.S.C. §103(a) as being unpatentable over Lassen or Johnson alone or in view of Remington. It is noted that neither Lassen nor Johnson gives a specific example teaching applicant's exact method. The Examiner urges that the skilled worker would be motivated to make an oral tablet based on the teachings in the cited references. The Examiner contends that no evidence has been provided to indicate that the cited art used one method of tableting over another.

In order to establish a *prima facie* case of obviousness, the prior art must (1) contain some teaching or motivation that would lead a person skilled in the art to modify the teachings of the reference in a manner that would produce the claimed invention, (2) show that there is a reasonable expectation of success in such a modification, and (3) teach or suggest all limitations of the claims. See MPEP 2143. Recently, the Federal Circuit has stated that evidence of a teaching, suggestion or motivation to modify must be "clear and particular". See In re Dembiczak, 50 USPQ2d 1614 (Fed. Cir. 1999).

Regarding the teachings in the cited references, applicants note that only Johnson is alleged to disclose the preparation of a single tablet. Lassen and Remington provide only general descriptions of how to make pharmaceutical formulations.

As indicated in the declaration of Dr. Doughty and the affidavit of Dr. Rhodes (or record), pharmaceutical tablets can be prepared by numerous processes and tablets that are prepared by different processes exhibit different and identifiable characteristics. Specifically, Dr.Rhodes, in paragraphs 29 to 31, describes how the content uniformity and compaction profile of the excipients in tablets will differ depending on the procedure used to make the tablet. In the case of paroxetine, Dr. Rhodes emphasizes that the reduction in the pink hue, realized when the dry process is used, is a characteristic which imparts a superior quality over the tablets made by the old conventional wet granulation process.

Applicants refer to the affidavit of Dr. Rhodes. Dr. Rhodes is a Professor of Applied Pharmaceutical Sciences at the University of Rhode Island. Professor

Rhodes has published approximately two hundred and fifty publications on a variety of pharmaceutical topics associated with the design and evaluation of drug delivery systems and devices. Applicants cite Dr. Rhodes' affidavit as the view of one skilled in the relevant art. As indicated in paragraphs 40 to 44 of Dr. Rhodes affidavit, the only example in Johnson providing a tablet formulation would lead one of skill in the art to make paroxetine tablets by wet granulation. According to Dr. Rhodes (paragraph 42 of the affidavit), the components of the Example 1 tablet formulation are those of the wet granulation commercial product as set forth in SmithKline's New Drug Application. Further, Example 1 of Johnson states that the excipients were mixed together in a conventional manner and compressed in a conventional manner. Dr. Rhodes indicates that, as of 1993, wet granulation was the conventional tableting process (paragraph 43 of the affidavit). He concludes that, when persons of skill in the art see the term "conventional" in Johnson at the time of Johnson, they would likely think of a wet granulation process. Moreover, the formulation of Example 1 includes "Hydroxypropylmethyl cellulose 2910" (hereinafter HPMC). HPMC is a common cellulose derivative and well known for its use as a wet binder. When HPMC is to be used as a wet binder, it generally makes up from about 5 to 10% weight/weight of the total tablet formulation. The weight of the tablet of Example 1 is 300 mg and includes 15 mg of HPMC, which is 5% of the total tablet weight. Dr. Rhodes concludes (paragraph 44 of his affidavit) that one of skill in the art would infer that the tablet of Example 1 in Johnson is a wet admixed paroxetine tablet.

Thus, in view of the above; specifically

a) that the components of Example 1 are the same as those in the wet granulated commercial product containing paroxetine,

b) that wet granulation was the conventional method of tablet formulation in 1993, and

c) that when HPMC is used as indicated in Example 1 (i.e. at about 5 to 10%) it indicates a wet granulation process is being used,

one of skill in the art would conclude that the tablet of Example 1 in Johnson was prepared using a wet granulation process and that the disclosed tablet is a wet admixed paroxetine tablet.

On page 3 of the outstanding Office Action, the Examiner states that Johnson is interpreted as suggesting dry mixing. However, the only reason given in the Office Action for this conclusion is that water is not mentioned in the example. Dr. Rhodes is a Professor of Applied Pharmaceutical Sciences and has offered a very detailed

affidavit as to why one skilled in the art would conclude that the tablet disclosed in Johnson was prepared using a wet granulation process. Applicants specifically request that the Examiner include in the record an analysis of Dr. Rhodes findings and expert opinions particularly in view of:

a) that the components of Example 1 are the same as those in the wet granulated commercial product containing paroxetine,

b) that wet granulation was the conventional method of tablet formulation in 1993, and

c) that when HPMC is used as indicated in Example 1 (i.e. at about 5 to 10%) it indicates a wet granulation process is being used.

Further, on page 4 of the outstanding Office Action, the Examiner states that "the example of Johnson ... teaches mixing the components listed in any conventional manner" (emphasis added). Applicants note that the phrase "in any conventional manner" doesn't appear in the Example in Johnson. The phrase "in a conventional manner" is used in Johnson. In view of the detailed affidavit of Dr. Rhodes, applicants specifically request that the Examiner state for the record how the example in Johnson can be interpreted as being directed to "any" conventional manner and not to a wet admixed product as concluded by Dr. Rhodes.

As indicated above, the single tablet alleged to be prepared in Johnson is described as being prepared by what the skilled worker would conclude is a wet granulation process. The remaining descriptions in Lassen, Johnson and Remington provide general boilerplate language on how to prepare pharmaceutical formulations. As such, there is no teaching in any of the cited references that specifically directs the skilled worker to a particular pharmaceutical tablet formulation. More importantly, the cited references fail to direct the skilled worker to applicants dry process to prepare pharmaceutical tablets containing paroxetine. Accordingly, there is no motivation to modify any of the applied references in a way that would produce the claimed tablets. The descriptions of the cited art lead the skilled worker to a wet granulated tablet (Johnson) or to a general description of how to make pharmaceutical formulations with no specific formulation (and with no specific tableting process) indicated. Thus, the cited art fails to provide a "clear and particular" suggestion or motivation to prepare applicants invention as required by In re Dembiczak, 50 USPQ2d 1614.

Regarding applicants comments indicating that all of the tablets sold have been formulated using a wet granulation process, this teaching is indicated in the specification (and in paragraph 8(ii) of the declaration of Dr. Doughty) by statements of those with personal knowledge. There is nothing in the teachings of Johnson, Lassen or Remington to lead a person skilled in the art away from a commercial wet granulation process to the dry process used to make the claimed tablets.

On page 6 of the outstanding Office Action, the Examiner states "Applicant is making a blanket and unsupported statement that all paroxetine formulations, *except their own*, have been made using wet granulation." "Absent evidence to support such a strong assertion, the Examiner relies on the above rejection."

The reason applicants can make the assertion that all paroxetine formulations have been made using wet granulation is that only SmithKline Beecham (or companies under its control) were making paroxetine formulations at the time of the invention. Early in the life cycle of a product, only the innovating company makes formulations because only the innovating company is investing time and money in the product. It is noted that the references cited as prior art during the prosecution of this application (except the general references such as Remington, which do not mention paroxetine) were assigned to SmithKline Beecham or a company that SmithKline Beecham collaborated with regarding paroxetine. Applicants make the statement that all formulations have been made using wet granulation from personal knowledge. Nothing in the record contradicts applicants statement.

Applicants specifically request that the Examiner state for the record why applicant's statements, about information within the scope or their own knowledge, is not acceptable to the Examiner, in the absence of any evidence the Examiner can state to the contrary.

All tablet formulations of paroxetine that were sold at the time of the invention were formulated using an aqueous granulation process. Applicants know this because only they were authorized to sell and selling paroxetine at this time. On a commercial scale, this process produces unacceptable formulations in that a highly undesirable pink hue is intermittently formed on a batch to batch basis. The current invention is directed to the unexpected discovery that the formulation of paroxetine into tablets can be carried out reliably and on a commercial scale using a formulation process in which water is absent.

It is a well established principle of patent law that unobviousness can reside in the discovery of the cause of a problem, the solution of which employs a combination of old elements. In re Sponnoble 160 USPQ 237 (CCPA 1969). The instant invention resulted from the discovery that the undesirable pink hue produced on a batch to batch basis when paroxetine was formulated via a wet granulation process was alleviated when the composition was formulated in the absence of water. As indicated by the affidavits of Dr. Rhodes and Dr. Roman (of record), this discovery was very surprising and resulted in a superior product. Applicants discovery of the problem is unexpected and their solution, using dry processing, is patentably unobvious over the cited references.

On page 6 of the outstanding Office Action, the Examiner states that "it is unclear what the claimed improvement is." The record is replete with statements, by affidavit and declaration, that switching from a wet process to a dry process unexpectedly saved time, bulk drug substance and a lot of money. The dry process did not eliminate the pink hue but alleviated it to the extent that a reliable and reproducible commercial scale process was discovered.

There is no requirements in the statutes that requires problems, such as the pink hue, to be eliminated in a patentability determination. If the Examiner disagrees, the Examiner is requested to cite the authority. What is required for nonobviousness is that the invention result in a unexpected advance or improvement over what one skilled in the art would expect. Again the record is replete with statements, by affidavit and declaration, that the instant invention was surprising and resulted in a superior product. According to In re Sponnoble, applicants' discovery of the problem is unexpected and their solution, using dry processing, is patentably unobvious over the cited references.

Applicants request that the Examiner state for the record why their stated improvements of saving time, money and resources, and the declarations and affidavits of record that indicate the discovery was unexpected, do not render their invention patentable under In re Sponnoble.

Applicants contend that it was highly unexpected to discover that the intermittent pink hue problem was ameliorated by removing water from the process, when water was always present in the process used to make the formulations of

paroxetine sold at that time. Further, as indicated in paragraphs 29 and 32 of Dr. Rhodes' affidavit, the tablets made by the dry process are different and superior to the tablets made by the wet process. Nothing in the cited references renders obvious applicants invention.

Finally, applicants object the Examiner's statement that Dr. Roman's declaration is considered misleading. Dr. Roman's declaration is very precise, very easy to follow and outlines the discovery process of the invention. The switch to a dry process resulted in the surprising improvement in tablet quality and bypassed the need to monitor impurities. This is another advantage of the claimed invention. The Examiner's open ended question about whether or not there is something more important about the impurity is misplaced and unjustified.

Applicants therefore submit that all reasons for rejection have been addressed and that the claims, as amended, are allowable. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned attorney at the number indicated below.

Respectfully submitted,

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